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nature

Basis for recognition of cisplatin-modified DNA by high-mobility group proteins.

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The anticancer activity of cis-diamminedichloroplatinum(II) (cisplatin) arises from its ability to damage DNA, with the major adducts formed being intrastrand d(GpCpG) crosslinks. These crosslinks bend and unwind the duplex, and the altered DNA structure attracts high-mobility-group domain (HMG) and other proteins. The ability of HMG-domain proteins to cisplatin-modified DNA has been postulated to be related to the antitumour properties of the drug. Many HMG-domain proteins recognize specific DNA structures such as four-way junctions and cisplatin-modified DNA, but the molecular basis for this recognition was unknown. Here we describe the structure of a 1:1 cisplatin-modified DNA/HMG-domain complex. Domain 1 of the structure-specific HMG-domain protein HMG1 binds to the widened minor groove of a 16-base-pair DNA duplex containing a site-specific cis-[Pt(NH₃)₂ d(GpCpG N7(2))] adduct. The DNA is strongly kinked at a hydrophobic notch created by the platinum-DNA crosslink and protein binding extends exclusively to the 3' side of the platinated strand. A phenylalanine residue at position 37 intercalates into a hydrophobic notch created at the platinum crosslinked d(GpCpG) site and binding of the domain is dramatically reduced in a mutant in which alanine is substituted for phenylalanine at this position.

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